REMARKS

I. Status of Claims

Claims 44-53 are pending in the instant case. Claims 44-45 stand rejected under 35 U.S.C. §112, first paragraph. Claims 45-53 are indicated as allowable if rewritten in independent format. Applicants traverse the rejection with respect to claims 44-45 and believe the response and amendments presented herein overcome these rejections and place the instant case in condition for allowance and an indication of such favorable action is solicited from the Examiner.

Claim 44 has been amended herein to provide further clarity to the claim. A marked up version of the amendment is provided attached as Appendix A. Applicants representative verifies that this amendment does not add new matter to the specification.

II. Formalities

Applicants acknowledge the Examiner's indication that the informal drawings are acceptable only for examination purposes and that formal drawings will be required upon allowance of the application. Applicants respectfully request that the formal drawing requirements be held in abeyance until allowance is indicated in this matter.

Applicants acknowledge the Examiner's comments regarding the use of trademarks in the specification. Applicants will provide a supplemental amendment in which any reference to trademarks in the specification is amended to comport with the requirements of United States Patent and Trademark Office practice. Applicants request that they be allowed to comply with this requirement in a subsequent submission.

III. Rejections under 35 U.S.C. §112, first paragraph should be withdrawn

Claims 44-45 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey that the inventors had possession of the claimed invention. Applicants respectfully traverse.

The rejection appears to be based on claims 44-45 encompassing any specific binding pair and the Examiner's contention (Paper 9, page 4, last paragraph) that: "the skilled artisan cannot envision the method of making libraries of other specific binding pairs which would be displayed on the surface of a filamentous phage". Applicants respectfully submit that this is a completely unsubstantiated assertion, without reliance on any technical facts or evidence.

The test for whether a particular claim is supported by the disclosure of an invention is to determine whether the disclosure, at the time of filing, contained sufficient information regarding the subject matter to enable one of skill in the art to make and use the claimed invention. A disclosure need not teach, and preferably should omit, what is well known to those of skill in the art. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). As long as the specification contains at least one method of making and using the claimed invention that bears a reasonable correlation to the entire scope of the claimed invention, then the enablement requirement under 35 U.S.C. §112 is satisfied. *In re Fisher*, 166 USPQ 18, 24 (CCPA, 1970); MPEP 2164.01(b).

As is discussed below, the specification contains much discussion of generation of libraries of sequences, including by means of *in vitro* mutagenesis as specifically claimed in claim 45. Both *in vitro* and *in vivo* mutagenesis of polypeptide specific binding pair members with subsequent display on the surface of filamentous bacteriophage particles are exemplified experimentally. Additional techniques for provision of genetically diverse populations of sequences are also discussed in the specification.

It is a plain fact that methods for generation of genetically diverse populations by mutagenesis can be applied to any nucleic acid sequence encoding any protein. The Examiner acknowledges that the specification is enabling for generation of genetically diverse populations of sequences providing a library encoding single chain antibodies (see Paper 9, page 4), and it logically follows that the specification is enabling for generation of genetically diverse populations of sequences encoding any specific binding pair members.

Any person of ordinary skill in the art reading the specification will note that various techniques for generation of genetically diverse populations have been described, including but not limited to *in vitro* and *in vivo* mutagenesis: *in vitro* mutagenesis to create a different specific binding pair member with different binding properties has been experimentally exemplified in Example 45; *in vivo* mutagenesis to create a different specific binding pair member with different binding properties has been experimentally exemplified in Example 38. The ordinary skilled person readily appreciates that the identical techniques are applicable to any polypeptide specific binding pair member.

It is fundamentally wrong that the "skilled artisan cannot envision the method of making the libraries of other specific binding pairs which would be displayed on the surface of a filamentous phage", as the Examiner asserts. The specification provides a plethora of Examples which describe actual experimental construction and use of a phagemid that expresses a gene fusion such *e.g.*, in Examples 17, 18, 19, 24, 25, 26, 27, 33, 38 and 44.

A claimed invention need not be described *ipsis verbis* in order to satisfy the requirements of 35 U.S.C. §112. *Ex parte Holt*, 19 U.S.P.Q.2d 1211, 1213 (B.P.A.I. 1991). The Examiner's attention is directed to Example 38, page 207-213 of the substitute specification which begins:

> "It will sometimes be desirable to increase the diversity of a pool of genes cloned in phage, for example a pool of antibody genes, or to produce a large number of

variants of a single cloned gene. There are many suitable *in vitro* mutagenesis methods."

The Example goes on to demonstrate experimental use of a mutator strain to mutate polypeptide-encoding sequences within vectors (*i.e.*, "genes cloned in phage"). As quoted, the specification also notes that "There are many suitable *in vitro* mutagenesis methods", indicating that the mutation of a gene sequence within a vector is not limited to mutation by means of a mutator strain.

See also page 14 of the substitute specification (lines 13-17), where a process is set out where a repertoire is first made before:

> "Libraries of pAbs could then be selected by binding to antigen, hypermutated *in vitro* in the antigen binding loops of V domain framework regions, and subjected to further rounds of selection and mutagenesis."

This indicates that the pAb libraries can be mutated within the antibody-encoding sequences. Note from page 13 of the description that "pAb" refers to the display article (whether antibody or other polypeptide is displayed), and the libraries subject to mutation and selection are made up of the display vectors. Moreover, Page 22 contains specific disclosure relating to enzymes: see the paragraph beginning "Another possibility, is the display of an enzyme molecule...". (Page 22, lines 3-14) See in particular:

> "If an enzyme with a different or modified specificity is described, it may be possible to mutate an enzyme displayed as a fusion on bacteriophage...", (Page 22, lines 9-11)

That is, the specification provides a teaching of mutating the sequence encoding the enzyme part of the fusion within the bacteriophage vector. Further, Example 32 provides the following observation with respect to experimental examples:

> "Thus mutagenesis of cloned enzymes expressed on the surface of filamentous bacteriophage will lead to a whole population of enzyme variants, from which variants with desired binding properties could be isolated."

The above discussion clearly demonstrates that the specification is replete with written support for the claimed invention. Applicants insist that irrespective of the nature of the polypeptide, the essentially the same methods can be used to mutate non-antibody polypeptides as for antibodies polypeptides, and these methods are fully disclosed in the specification as filed. Applicants respectfully request that in light of the above discussion, the rejection based on 35 U.S.C. §112, first paragraph be withdrawn.

IV. Conclusion

The applicants respectfully submit that the claims are in condition for allowance and early notification thereof is solicited. The examiner is invited to telephone the undersigned to discuss any remaining issues so as to expedite the progress of this case toward allowance.

Respectfully submitted,

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APPENDIX A
MARKED UP VERSION OF AMENDMENT TO CLAIMS

44. (Twice Amended) Recombinant host cells which each harbor a nucleic acid fragment encoding a specific binding pair member whereby the host cells collectively harbor ~~harboring~~ a library of nucleic acid fragments comprising fragments encoding a genetically diverse population of ~~a member of a~~ specific binding pair members, each specific binding pair member being expressed as a fusion with a gene III coat protein surface component of a filamentous bacteriophage so that said specific binding pair members are displayed on the surface of bacteriophage particles ~~in functional form comprising~~ and comprise a binding domain for its complementary specific binding pair member, and genetic material of each particle displaying a specific binding pair member encodes its associated displayed specific binding pair members, said genetic material being a phagemid genome which is plasmid nucleic acid containing a single stranded phage replication origin and a nucleotide sequence encoding ~~a~~ said fusion and wherein said genetic material is packaged into particles by a helper phage whereby each particle has a coat partially derived from the helper phage and partly from said fusion.